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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,753	10/09/2003	Christopher G. Williams	14977-0139	8131

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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
04/05/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/681,753	WILLIAMS ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2010*.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-63,65-77 and 88* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *53-63,65-77 and 88* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *12/29/2010*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 12/20/2010.

Claims 53 and 66 have been amended. Claim 88 has been newly added. No claims have been newly canceled.

Claims 53-63, 65-77 and 88 are currently pending and have been examined on their merits.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62 and 76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have entered the limitation “in direct contact” in claims 53 and 66 which requires that the hydrogel layers are placed in direct contact with each other. Claims 53 and 66 require that a suspension of cells be added to a surface of a hydrogel prior to the placement of the next hydrogel layer. There is no description in Applicant’s disclosure wherein the hydrogel layers maintain direct contact with each other in spite of a cell suspension being added between them and therefore there is not sufficient support in the disclosure as originally filed for this limitation; thus it is being considered new matter. The disclosure as originally filed only supports embodiments wherein the hydrogels are placed in direct contact with each other OR wherein the hydrogels are placed with a cell suspension added between each hydrogel layer such that a cell layer is formed between the hydrogel layers (see original claim 47). An embodiment wherein the hydrogels are placed in direct contact with each other but have a cell suspension placed between them is not disclosed and is considered new matter.

An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed. In re Wright, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989). Applicant is required to cancel the new matter in the reply to this Office Action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims require an additional step of adding a suspension of cells to a surface of the first hydrogel before the step of placing the second hydrogel in the tissue space which appears to be contradictory to the independent claims 53 and 66 which require direct contact between the hydrogel layers. It is unclear from Applicant's disclosure as there is no description of how one was to keep the hydrogels in direct contact when there is a layer of cells between them.

Appropriate correction and clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53-61,63, 65-75, 77 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vacanti (US 5,944,754) in view of Sah et al (US 2003/0077821), Anseth et al (Journal of Controlled Release 2002), Cooke et al (US 5,916,585) and Spiro et al (US 6,773,723).

Amended claim 53 is drawn to a method of producing a multi-layered tissue construct *in vivo* comprising: providing a first polymerizable mixture which comprises a first polymerizable material and first cells and directly placing a volume of the first polymerizable mixture in an osteochondral tissue space wherein the first polymerizable mixture is in direct contact with the osteochondral tissue underneath, then crosslinking the first polymerizable mixture until the first polymerizable mixture material is at least partially gelled to form a first layer of hydrogel;

providing a second polymerizable mixture which comprises a second polymerizable material and directly placing a volume of the second polymerizable mixture in the tissue space in direct contact with the at least partially gelled first layer of hydrogel, then crosslinking the second polymerizable mixture until the second polymerizable mixture material is at least partially gelled to form a second layer of hydrogel;

additionally crosslinking the first and second polymerizable materials until the layers further polymerize to form an integrated multi-layered hydrogel; wherein the first and second hydrogels each independently consist essentially of a hydrophilic and synthetic polymer network with high water content.

Dependent claims include the types of cells used, addition of bioactive substances, wherein crosslinking is controlled by exposure to external radiation and an additional step of adding a suspension of cells to a surface of the partially gelled first layer before the step of placing the second polymerizable mixture in the tissue space.

Amended claim 66 is now drawn to a method of producing a multi-layered tissue construct *in vivo* comprising:

providing a first polymerizable mixture which comprises a first polymerizable material and first cells and directly placing a volume of the first polymerizable mixture in an osteochondral tissue space wherein the first polymerizable mixture is in direct contact with the osteochondral tissue underneath, then crosslinking the first polymerizable mixture until the first polymerizable mixture material is at least partially gelled to form a first layer of hydrogel;

providing a second polymerizable mixture which comprises a second polymerizable material and directly placing a volume of the second polymerizable mixture in the tissue space in direct contact with the at least partially gelled first layer, then crosslinking the second polymerizable mixture until the second polymerizable mixture material is at least partially gelled to form a second layer of hydrogel;

providing a third polymerizable mixture which comprises a third polymerizable material and directly placing a volume of the third polymerizable mixture in the tissue space in direct contact with the at least partially gelled ~~first and~~ second layer, then crosslinking the third polymerizable mixture until the third polymerizable mixture material is at least partially gelled to form a third layer;

wherein at least one of the second and third polymerizable mixtures further comprises cells;

additionally crosslinking the first and second polymerizable materials until the layers further polymerize to form an integrated multi-layered hydrogel; wherein the first, second and third hydrogels each independently consist essentially of a hydrophilic and synthetic polymer network with high water content.

Dependent claims include the types of cells used, addition of bioactive substances and a polymerization initiator and the formation of the layers.

New claim 88 is drawn to a method of producing a multi-layered tissue construct in vivo wherein the polymerizable mixtures are directly placed by injection.

The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.” See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 (“PPG could have defined the scope of the phrase ‘consisting essentially of’ for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.”).

The term “directly placing a volume of polymerizable mixture” is interpreted to include any manner of placing the polymerizable material such that it allows for direct contact with the target tissue for repair.

Vacanti teaches a method for re-surfacing with hydrogel-cell compositions. The process of placing a polymer material in a lesion (*in vivo*) comprising a joint (subchondral bone) *in situ* is taught and shows *in vivo* production of a hydrogel cell constructed tissue construct (column 2 lines 18-51). Solidification of the hydrogel occurs by crosslinking (column 3 lines 35-41). Suitable polymerizable materials include synthetic polymers (column 4 lines 10-65) such as those taught by Applicant (i. e. polyethylene glycol-Applicant’s Specification page 27 paragraph 110).

Cells are preferably autologous and include chondrocytes and other cells that form cartilage and osteoblasts and other cells that form bone (column 7 lines 19-54). A hydrogel-cell composition that has two layers including different cell types in each layer is described for embodiments wherein skin tissue is repaired (column 9 lines 25-35) and allows for the first hydrogel to solidify (crosslink/polymerize) before the second hydrogel is added (column 13 example 8). Hydrogels are taught to be set by exposure to either visible or ultraviolet light (column 4 lines 25-30 and column 6 lines 45-67). The mimicking of the tissue to be generated is suggested as desirable (column 7 lines 64-67). Introduction of the hydrogel-cell composition through a laparoscope or endoscope is suggested as suitable (column 8 lines 48-63).

Vacanti does not specifically teach a multi-layered hydrogel composition for an osteochondral tissue space. Vacanti does not teach administering the hydrogel compositions by injection. While the viability of the cells is taught as important, Vacanti does not specifically teach the addition of growth factors with the hydrogel-cell compositions.

Vacanti does not specifically teach producing the construct with a photoinitiator, mixing the polymer with a third cell types for *in vivo* formation of the construct or additionally crosslinking until the layers further polymerize to form an integrated multi-layered matrix.

Sah et al teaches methods of forming engineered stratified cartilage tissue and states that “supplying cells with proper zonal phenotype to their respective zones in engineered tissue can reduce the time of tissue maturation by reducing the need for cellular migration and/or differentiation in the tissue” (page 11 para 96). An engineered construct with stratification that mimics native cartilage is taught to be particularly useful for repair of cartilage defects (page 11 para 97). Sah et al includes chondrogenic cells in each layer of the engineered construct (page 11, claim 1) as well as additional cells in the first layer (page 3 para 29) and teaches that additional layers are not to be added until the current layer coalesces (page 9 para 82). The use of different types of chondrocytes is also taught (page 3 para 30).

One of ordinary skill in the art would have been motivated to include a multi-layered hydrogel-cell construct with each layer polymerized separately for osteochondral defects (bone/cartilage tissue sites such as joints) in the method of Vacanti because Sah et al teach that "supplying cells with proper zonal phenotype to their respective zones in engineered tissue can reduce the time of tissue maturation by reducing the need for cellular migration and/or differentiation in the tissue". One of ordinary skill in the art would have used different types of cells or the same types of cells as Vacanti teaches that either is an option in a multi-layered hydrogel-cell composition (column 13 example 8). One of ordinary skill in the art would have had a reasonable expectation of success because Vacanti was already using a multi-layered approach for the repair of tissue such as skin.

Anseth teaches that medical applications benefit from the ability to fabricate polymers *in situ* such that adhesion of the polymer to surrounding tissue is generally significantly improved because of intimate contact of the polymer with the tissue during formation and the resulting mechanical interlocking that can arise from surface microroughness. In addition, the invasiveness of some surgical techniques is minimized as liquid solutions are easily introduced through needle injections and can be photocured with fiber optic cables using arthroscopic techniques (page 200 column 1). Photoinitiated polymerizations overcome many limitations of *in situ* polymerization since the initiation does not require elevated temperatures, and the polymerization rate is sufficiently rapid, occurring over a short time period, which allows the system to overcome oxygen inhibition and moisture effects (page 200 column 1). In tissue cartilage engineering, photopolymerization provides many benefits including rapid polymerization times under physiological conditions with temporal and spatial control over the polymerization. *In situ* forming hydrogels are attractive for their high water content and tissue-like elastic properties (page 207, column 1).

One of ordinary skill in the art would have been motivated to include a photoinitiator in the method of Vacanti because Anseth teach that they are suitable for polymerizing encapsulated cells in the repair of cartilaginous tissue and Vacanti is also teaching cartilage repair with photopolymerizable hydrogels. One of ordinary skill in the art would have had a reasonable expectation of success because Vacanti suggests the use of chemicals and radiation for solidifying the cellular support matrix (column 4).

One of ordinary skill in the art would have been motivated to mix the polymer with second or third cells for *in vivo* formation of the construct or additionally crosslinking to form an integrated multi-layered matrix in vivo as opposed to the formation of such constructs *in vitro* (as described by Sah) because Anseth teaches the advantages of *in situ* (and inherently *in vivo*) formation of an engineered tissue construct. One of ordinary skill in the art would have had a reasonable expectation of success because Vacanti does teach at least one embodiment with *in vivo* formation of the multi-layered tissue construct and the prior art references teach that methods using hydrogels for tissue engineering and photopolymerization are successful in the repair of cartilaginous tissue.

One of ordinary skill in the art would have been motivated to administer the hydrogel-cell composition by injection in the method of Vacanti because Anseth teach that this is a suitable manner in which to administer such a composition. One of ordinary skill in the art would have had a reasonable expectation of success because both Vacanti and Anseth teach the use of arthroscopic techniques to facilitate the administration and in vivo formation of their hydrogel compositions.

Cooke et al teach materials and methods for the immobilization of bioactive species onto biodegradable polymers. The bioactive species are taught to include mammalian cells (column 4 lines 5-16) and multi-layered polymers wherein the layers are crosslinked by photon irradiation (column 13 lines 34-column 14 lines 23) are also taught to be desirable as well. Growth factors are taught to beneficial additives for their ability to promote proliferation or differentiation of cellular bioactive species (column 6 lines 63-67).

Spiro et al teach bilayer matrices for tissue regeneration wherein the layers are attached to each other by either mechanical adhesion or chemical cross-linking by cross-linking agents (column 1 lines 30-58). The addition of growth factors (column 2 lines 40-67) as well as autologous cells encapsulated within the matrix are taught as well (column 3 lines 1-15). Application of the matrices at an osteochondral site is also taught (column 4 lines 5-14). Bone marrow and bone marrow stromal cells (which inherently include mesenchymal stem cells) are the source of chondro-progenitor cells found in the subchondral bone marrow of full thickness defects and are taught to be a suitable source for use in a multilayered hydrogel construct for repair of bone and cartilage tissue (column 4 lines 33-36).

Therefore, one of ordinary skill in the art would have been motivated to attach the layers of the multi-layered construct of Vacanti by further crosslinking the layers as both Cooke et al and Spiro et al teach that this is a desirable step in the formation of a multi-layered polymer construct intended for tissue repair. One of ordinary skill in the art would have been motivated to use photon irradiation for the cross-linking because Cooke et al teach that this is a suitable catalyst for crosslinking multi-layered constructs (column 14 lines 6-11). One of ordinary skill in the art would have had a reasonable expectation of success because Vacanti, Cooke et al and Spiro et al were all drawn to making multi-layered polymer constructs for tissue regeneration using many of the same polymers and cell types.

One of ordinary skill in the art would have been motivated to use mesenchymal stem cells in the method of Vacanti because Vacanti teaches that cells that will form cartilage and bone are useful in the method. One of ordinary skill in the art would have had a reasonable expectation of success because Spiro teach that bone marrow and bone marrow stromal cells, which inherently include mesenchymal stem cells, are suitable sources of chondro-progenitor cells (cells that will become chondrocytes as well as bone).

Therefore, the combined teachings of Vacanti, Sah et al, Anseth et al, Cooke et al and Spiro et al render obvious Applicant’s invention as claimed.

Response to Arguments

Applicant's arguments with respect to claims 53-63, 65-77 and 88 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura Schuberg/
Primary Examiner
Art Unit 1657